REMARKS

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "Version with markings to show changes made."

Applicants reserve the right to prosecute non-elected subject matter in subsequent divisional applications.

I. Restriction requirement/election

Election, with traverse, of the claims of Group II (encompassing claims 3-7, 9, 10, 12, 13, 46, and 57), directed to polynucleotides, vectors, host cells, microarrays, and methods of using the polynucleotides to produce the encoded polypeptides, is acknowledged. Applicants respectfully point out that claims 58 and 59 should be included in the claims of Group II because they are directed to polynucleotides of the invention. In particular, claim 58 depends from claim 12 and is directed to a subset of the polynucleotides recited by claim 12. Similarly, claim 59 depends from claim 13 and is directed to a subset of the polynucleotides recited by claim 13.

Applicants thank the Examiner for acknowledging that, upon allowance of the product claims, rejoinder of process claims commensurate in scope with the allowed product claims will be considered.

II. Utility rejection under 35 U.S.C. § 101

The rejection of claims 3-7, 9, 10, 12, 13, 46, and 57 is improper, as the inventions of those claims have a patentable utility as set forth in the instant specification, and/or a utility well-known to one of ordinary skill in the art.

The invention at issue is a polynucleotide sequence corresponding to a gene that is expressed in breast, lung, lymphocyte, macrophage, bladder tumor, NIDDM pancreas, and rheumatoid synovium tissues of humans (Specification, e.g., at page 5, lines 12-23; page 6, lines 2-4; page 30, lines 18-29; and Figure 5). The claimed polynucleotide encodes a polypeptide demonstrated in the patent specification to be a member of the CC chemokine protein family, whose biological functions include

generating gradients of chemoattractant factors which activate, and may cause the proliferation of, specific cell types such as monocytes, macrophages, basophils, eosinophils, T lymphocytes, and fibroblasts (e.g., at page 1, lines 25-35; and page 2, lines 21-25). As such, the claimed invention has numerous practical, beneficial uses in toxicology testing, drug development, and the diagnosis of disease, none of which require knowledge of how the polypeptide encoded by the claimed polynucleotide actually functions. As a result of the benefits of these uses, the claimed invention already enjoys significant commercial success.

Applicants submit with this response the declaration of Dr. Tod Bedilion describing some of the practical uses of the claimed invention in gene and protein expression monitoring applications. The Bedilion Declaration demonstrates that the positions and arguments made by the Office Action with respect to the utility of the claimed polynucleotide are without merit.

The Bedilion Declaration describes, in particular, how the claimed expressed polynucleotides can be used in gene expression monitoring applications that were well-known at the time the patent application was filed, and how those applications are useful in developing drugs and monitoring their activity. Dr. Bedilion states that the claimed invention is a useful tool when employed as highly specific probes in a cDNA microarray:

> Persons skilled in the art would [on July 15, 1996] appreciate that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for cancer and inflammatory disorders for such purposes as evaluating their efficacy and toxicity. (Bedilion Declaration, ¶ 15)

The Office Action does not dispute that the claimed polynucleotides can be used as probes in cDNA microarrays and used in gene expression monitoring applications. Instead, the Office Action contends that the claimed polynucleotides cannot be useful without precise knowledge of their biological functions, or the biological functions of their encoded polypeptide. But the law never has required knowledge of biological function to prove utility. It is the claimed invention's uses, not its functions, that are the subject of a proper analysis under the utility requirement.

In any event, as demonstrated by the Bedilion Declaration, the person of ordinary skill in the art can achieve beneficial results from the claimed polynucleotides in the absence of any knowledge as to

the precise function of the protein encoded by them. The uses of the claimed polynucleotides in gene expression monitoring applications are in fact independent of their precise biological functions.

I. The Applicable Legal Standard

To meet the utility requirement of sections 101 and 112 of the Patent Act, the patent applicant need only show that the claimed invention is "practically useful," *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) and confers a "specific benefit" on the public. *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966). As discussed in a recent Court of Appeals for the Federal Circuit case, this threshold is not high:

> An invention is "useful" under section 101 if it is capable of providing some identifiable benefit. See *Brenner v. Manson*, 383 U.S. 519, 534 [148 USPQ 689] (1966); *Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 [24 USPQ2d 1401] (Fed. Cir. 1992) ("to violate Section 101 the claimed device must be totally incapable of achieving a useful result"); *Fuller v. Berger*, 120 F. 274, 275 (7th Cir. 1903) (test for utility is whether invention "is incapable of serving any beneficial end").

Juicy Whip Inc. v. Orange Bang Inc., 51 USPQ2d 1700 (Fed. Cir. 1999).

While an asserted utility must be described with specificity, the patent applicant need not demonstrate utility to a certainty. In *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), the United States Court of Appeals for the Federal Circuit explained:

> An invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is only operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.*, 730 F.2d 753, 762, 221 USPQ 473, 480 (Fed. Cir. 1984).

The specificity requirement is not, therefore, an onerous one. If the asserted utility is described so that a person of ordinary skill in the art would understand how to use the claimed invention, it is sufficiently specific. See *Standard Oil Co. v. Montedison, S.p.a.*, 212 U.S.P.Q. 327, 343 (3d Cir. 1981). The specificity requirement is met unless the asserted utility amounts to a "nebulous expression" such as "biological activity" or "biological properties" that does not convey meaningful information about the utility of what is being claimed. *Cross* v. *Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985).

In addition to conferring a specific benefit on the public, the benefit must also be "substantial." *Brenner*, 383 U.S. at 534. A "substantial" utility is a practical, "real-world" utility. *Nelson v. Bowler*, 626 F.2d 853, 856, 206 USPQ 881 (CCPA 1980).

If persons of ordinary skill in the art would understand that there is a "well-established" utility for the claimed invention, the threshold is met automatically and the applicant need not make any showing to demonstrate utility. Manual of Patent Examining Procedure at § 706.03(a). Only if there is no "well-established" utility for the claimed invention must the applicant demonstrate the practical benefits of the invention. *Id.*

Once the patent applicant identifies a specific utility, the claimed invention is presumed to possess it. *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999); *In re Brana*, 51 F.3d 1560, 1566; 34 USPQ2d 1436 (Fed. Cir. 1995). In that case, the Patent Office bears the burden of demonstrating that a person of ordinary skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention. *Id.* To do so, the Patent Office must provide evidence or sound scientific reasoning. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). If and only if the Patent Office makes such a showing, the burden shifts to the applicant to provide rebuttal evidence that would convince the person of ordinary skill that there is sufficient proof of utility. *Brana*, 51 F.3d at 1566. The applicant need only prove a "substantial likelihood" of utility; certainty is not required. *Brenner*, 383 U.S. at 532.

II. Toxicology testing, drug discovery, and disease diagnosis are sufficient utilities under 35 U.S.C. §§ 101 and 112, first paragraph

The claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law: There are "well-established" uses for the claimed invention known to persons of ordinary skill in the art, and there are specific practical and beneficial uses for the invention disclosed in the patent application's specification. These uses are explained, in detail, in the Bedilion Declaration accompanying this response. Objective evidence, not considered by the Patent Office, further corroborates the credibility of the asserted utilities.

A. The use of the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are practical uses that confer "specific benefits" to the public

The claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. These uses are explained in detail in the accompanying Bedilion Declaration, the substance of which is not rebutted by the Office Action. There is no dispute that the claimed invention is in fact a useful tool in cDNA microarrays used to perform gene expression analysis. That is sufficient to establish utility for the claimed polynucleotides.

The instant application is a continuation of, and claims priority to, Coleman et al. (U.S. Ser. No. 08/683,655, filed July 15, 1996; hereinafter "the Coleman '655 application"). The instant application and the Coleman '655 application were filed with essentially identical specifications, with the exception of corrected typographical errors and reformatting. Thus page and line numbers may not match as between the instant application and the Coleman '655 application.

In his Declaration, Dr. Bedilion explains the many reasons why a person skilled in the art reading the Coleman '655 application on July 15, 1996 would have understood that application to disclose the claimed polynucleotides to be useful for a number of gene expression monitoring applications, *e.g.*, as highly specific probes for the expression of those specific polynucleotides in connection with the development of drugs and the monitoring of the activity of such drugs (Bedilion Declaration at, e.g., ¶¶ 10-15). Much, but not all, of Dr. Bedilion's explanation concerns the use of the claimed polynucleotides in cDNA microarrays of the type first developed at Stanford University for evaluating the efficacy and toxicity of drugs, as well as for other applications (Bedilion Declaration, ¶¶ 12 and 15).[1]

In connection with his explanations, Dr. Bedilion states that "the specification of the Coleman '655 application would have led a person skilled in the art on July 15, 1996, who was using gene

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[1]Dr. Bedilion also explained, for example, why persons skilled in the art would also appreciate, based on the Coleman '655 specification, that the claimed polynucleotides would be useful in connection with developing new drugs using technology, such as Northern analysis, that predated by many years the development of the cDNA technology (Bedilion Declaration, ¶ 16).

expression monitoring in connection with developing new drugs for the treatment of cancer and inflammatory disorders, to conclude that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a highly useful tool and to request specifically that any cDNA microarray that was being used for such purposes contain the SEQ ID NO:1-encoding polynucleotides" (Bedilion Declaration, ¶ 15). For example, as explained by Dr. Bedilion, "[p]ersons skilled in the art would [on July 15, 1996] appreciate that a cDNA microarray that contained the SEQ ID NO:1-encoding polynucleotides would be a more useful tool than a cDNA microarray that did not contain any of these polynucleotides, in connection with conducting gene expression monitoring studies on proposed (or actual) drugs for cancer and inflammatory disorders, for such purposes as evaluating their efficacy and toxicity." *Id.*

In support of those statements, Dr. Bedilion provided detailed explanations of how cDNA technology can be used to conduct gene expression monitoring evaluations, with extensive citations to pre- and post-July 1996 publications showing the state of the art on July 15, 1996 (Bedilion Declaration, ¶¶ 10-14). While Dr. Bedilion's explanations in paragraph 15 of his Declaration include almost three pages of text and six subparts (a)-(f), he specifically states that his explanations are not "all-inclusive." *Id.* For example, with respect to toxicity evaluations, Dr. Bedilion had earlier explained how persons skilled in the art who were working on drug development on July 15, 1996 (and for several years prior to July 15, 1996) "without any doubt" appreciated that the toxicity (or lack of toxicity) of any proposed drug was "one of the most important criteria to be considered and evaluated in connection with the development of the drug" and how the teachings of the Coleman '655 application clearly include using differential gene expression analyses in toxicity studies (Bedilion Declaration, ¶ 10).

Thus, the Bedilion Declaration establishes that persons skilled in the art reading the Coleman '655 application at the time it was filed "would have wanted their cDNA microarray to have a probe to a SEQ ID NO:1-encoding polynucleotide because a microarray that contained such a probe (as compared to one that did not) would provide more useful results in the kind of gene expression monitoring studies using cDNA microarrays that persons skilled in the art have been doing since well prior to July 15, 1996" (Bedilion Declaration, ¶ 15, item (f)). This, by itself, provides more than sufficient reason to compel the conclusion that the Coleman '655 application disclosed to persons

skilled in the art at the time of its filing substantial, specific and credible real-world utilities for the claimed polynucleotides.

Nowhere does the Office Action address the fact that, as described, for example, on pages 14 and 20 of the Coleman '655 application (corresponding to pages 15 and 22 of the instant application), the claimed polynucleotides can be used as highly specific probes in, for example, cDNA microarrays – probes that without question can be used to measure both the existence and amount of complementary RNA sequences known to be the expression products of the claimed polynucleotides. The claimed invention is not, in that regard, some random sequence whose value as a probe is speculative or would require further research to determine.

Given the fact that the claimed SEQ ID NO:2 polynucleotide is known to be expressed, its utility as a measuring and analyzing instrument for expression levels is as indisputable as a scale's utility for measuring weight. This use as a measuring tool, regardless of how the expression level data ultimately would be used by a person of ordinary skill in the art, by itself demonstrates that the claimed invention provides an identifiable, real-world benefit that meets the utility requirement. *Raytheon* v. *Roper*, 724 F.2d 951, (Fed. Cir. 1983) (claimed invention need only meet one of its stated objectives to be useful); *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) (how the invention works is irrelevant to utility); M.P.E.P. § 2107.01 ("Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific, and unquestionable utility (e.g., **they are useful in analyzing compounds**)" (emphasis added)).

Though Applicants need not so prove to demonstrate utility, there can be no reasonable dispute that persons of ordinary skill in the art have numerous uses for information about relative gene expression including, for example, understanding the effects of a potential drug for treating cancer and inflammatory disorders. Because the patent application states explicitly that the claimed polynucleotide is known to be expressed both in normal cells as well as cells involved in cancer and other diseases (see the instant application at, e.g., page 5, lines 12-23; and Figure 5), there can be no reasonable dispute that a person of ordinary skill in the art could put the claimed invention to such use. In other words, the person of ordinary skill in the art can derive more information about a potential drug

candidate for cancer and inflammatory disorders, or potential toxin, with the claimed invention than without it (see Bedilion Declaration at, e.g., ¶ 15, subparts (e)-(f)).

The Bedilion Declaration shows that a number of pre- and post-July 15, 1996 publications confirm and further establish the utility of cDNA microarrays in a wide range of drug development gene expression monitoring applications at the time the Coleman '655 application was filed (Bedilion Declaration ¶¶ 10-14; and Tabs A-G). Indeed, Brown and Shalon U.S. Patent No. 5,807,522 (the Brown '522 patent, Bedilion Declaration at Tab D), which issued from a patent application filed in June 1995 and was effectively published on December 29, 1995 as a result of the publication of a PCT counterpart application, shows that the Patent Office recognizes the patentable utility of the cDNA technology developed in the early to mid-1990s. As explained by Dr. Bedilion, among other things (Bedilion Declaration, ¶ 12):

> The Brown '522 patent further teaches that the "[m]icroarrays of immobilized nucleic acid sequences prepared in accordance with the invention" can be used in "numerous" genetic applications, including "monitoring of gene expression" applications (see Tab D at col. 14, lines 36-42). The Brown '522 patent teaches (a) monitoring gene expression (i) in different tissue types, (ii) in different disease states, and (iii) in response to different drugs, and (b) that arrays disclosed therein may be used in toxicology studies (see Tab D at col. 15, lines 13-18 and 52-58; and col. 18, lines 25-30).

Literature reviews published after the filing of the Coleman '655 application describing the state of the art further confirm the claimed invention's utility. Rockett et al. confirm, for example, that the claimed invention is useful for differential expression analysis regardless of how expression is regulated:

> Despite the development of multiple technological advances which have recently brought the field of gene expression profiling to the forefront of molecular analysis, recognition of the importance of differential gene expression and characterization of differentially expressed genes has existed for many years.
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> * * *
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> Although differential expression technologies are applicable to a broad range of models, perhaps their most important advantage is that, in most cases, absolutely no prior knowledge of the specific genes which are up- or down-regulated is required.
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> * * *

> Whereas it would be informative to know the identity and functionality of all genes up/down regulated by . . . toxicants, this would appear a longer term goal . . . . However, the current use of gene profiling yields a **pattern** of gene changes for a xenobiotic of unknown toxicity which may be matched to that of well characterized toxins, thus alerting the toxicologist to possible in vivo similarities between the unknown and the standard, thereby providing a platform for more extensive toxicological examination. [emphasis added]

Rockett et al., Differential gene expression in drug metabolism and toxicology: Practicalities, problems and potential, Xenobiotica, 1999, 29:655-691.

In another article, Lashkari et al. state explicitly that sequences that are merely "predicted" to be expressed (predicted Open Reading Frames, or ORFs) – the claimed invention in fact is known to be expressed – have numerous uses:

> Efforts have been directed toward the amplification of each predicted ORF or any other region of the genome ranging from a few base pairs to several kilobase pairs. There are many uses for these amplicons– they can be cloned into standard vectors or specialized expression vectors, or can be cloned into other specialized vectors such as those used for two-hybrid analysis. **The amplicons can also be used directly by, for example, arraying onto glass for expression analysis**, for DNA binding assays, or for any direct DNA assay. [emphasis added]

Lashkari et al., Whole genome analysis: Experimental access to all genome sequenced segments through larger-scale efficient oligonucleotide synthesis and PCR, Proceedings of the National Academy of Sciences USA, 1997, 94:8945-8947.

B. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of disease is now "well-established"

The technologies made possible by expression profiling and the DNA tools upon which they rely are now well-established. The technical literature recognizes not only the prevalence of these technologies, but also their unprecedented advantages in drug development, testing and safety assessment. These technologies include toxicology testing, as described by Dr. Bedilion in his declaration.

Toxicology testing is now standard practice in the pharmaceutical industry. See, *e.g.*, John C. Rockett et al., *supra*:

> Knowledge of toxin-dependent regulation in target tissues is not solely an academic pursuit as much interest has been generated in the pharmaceutical industry to harness this technology in the early identification of toxic drug candidates, thereby shortening the developmental process and contributing substantially to the safety assessment of new drugs. (Rockett et al., page 656)

To the same effect are several other scientific publications, including Emile F. Nuwaysir et al., Microarrays and toxicology: The advent of toxicogenomics, Molecular Carcinogenesis, 1999, 24:153-159; Sandra Steiner and N. Leigh Anderson, Expression profiling in toxicology – potentials and limitations, Toxicology Letters, 2000, 112-113:467-471.

> Nucleic acids useful for measuring the expression of whole classes of genes are routinely incorporated for use in toxicology testing. Nuwaysir et al. describes, for example, a Human ToxChip comprising 2089 human clones, which were selected
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> > for their well-documented involvement in basic cellular processes as well as their responses to different types of toxic insult. Included on this list are DNA replication and repair genes, apoptosis genes, and genes responsive to PAHs and dioxin-like compounds, peroxisome proliferators, estrogenic compounds, and oxidant stress. Some of the other categories of genes include transcription factors, oncogenes, tumor suppressor genes, cyclins, kinases, phosphatases, cell adhesion and motility genes, and homeobox genes. Also included in this group are 84 housekeeping genes, whose hybridization intensity is averaged and used for signal normalization of the other genes on the chip.

See also Table 1 of Nuwaysir et al. (listing additional classes of genes deemed to be of special interest in making a human toxicology microarray).

> The more genes that are available for use in toxicology testing, the more powerful the technique. "Arrays are at their most powerful when they contain the entire genome of the species they are being used to study." John C. Rockett and David J. Dix, Application of DNA arrays to toxicology, Environmental Health Perspectives, 1999, 107:681-685. Control genes are carefully selected for their stability across a large set of array experiments in order to best study the effect of toxicological compounds. See attached email from the primary investigator of the Nuwaysir paper, Dr. Cynthia Afshari to an Incyte employee, dated July 3, 2000, as well as the original message to which she was responding. Thus, there is no expressed gene which is irrelevant to screening for toxicological effects, and all expressed genes have a utility for toxicological screening.

In fact, the potential benefit to the public, in terms of lives saved and reduced health care costs, are enormous. Recent developments provide evidence that the benefits of this information are already beginning to manifest themselves. Examples include the following:

- In 1999, CV Therapeutics, an Incyte collaborator, was able to use Incyte gene expression technology, information about the structure of a known transporter gene, and chromosomal mapping location, to identify the key gene associated with Tangiers disease. This discovery took place over a matter of only a few weeks, due to the power of these new genomics technologies. The discovery received an award from the American Heart Association as one of the top 10 discoveries associated with heart disease research in 1999.

- In an April 9, 2000, article published by the Bloomberg news service, an Incyte customer stated that it had reduced the time associated with target discovery and validation from 36 months to 18 months, through use of Incyte's genomic information database. Other Incyte customers have privately reported similar experiences. The implications of this significant saving of time and expense for the number of drugs that may be developed and their cost are obvious.

- In a February 10, 2000, article in the *Wall Street Journal*, one Incyte customer stated that over 50 percent of the drug targets in its current pipeline were derived from the Incyte database. Other Incyte customers have privately reported similar experiences. By doubling the number of targets available to pharmaceutical researchers, Incyte genomic information has demonstrably accelerated the development of new drugs.

Because the Office Action failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and the diagnosis of disease, the rejections should be withdrawn regardless of their merit.

C. The similarity of the polypeptide encoded by the claimed invention to another polypeptide of undisputed utility demonstrates utility

In addition to having substantial, specific and credible utilities in numerous gene expression monitoring applications, the utility of the claimed polynucleotides can be imputed based on the relationship between the polypeptide they encode, MCPP, and other polypeptides of unquestioned utility, the CC chemokines hJE-2/MCP-2 (GenBank ID 338009) and MCP-3 (GenBank ID 288397). The polypeptides have sufficient similarities in their sequences that a person of ordinary skill in the art

would recognize more than a reasonable probability that the polypeptide encoded for by the claimed invention has utility similar to the CC chemokines hJE-2/MCP-2 and MCP-3. Applicants need not show any more to demonstrate utility. *In re Brana*, 51 F.3d at 1567.

It is undisputed that the polypeptide coded for by the claimed polynucleotides shares 63% sequence identity with hJE-2/MCP-2 and 62% sequence identity with MCP-3, over 109 amino acid residues (Specification, e.g., page 5, lines 27-31; and Figure 2). This is more than enough homology to demonstrate a reasonable probability that the utility of the CC chemokines hJE-2/MCP-2 and MCP-3 can be imputed to the polynucleotides of the claimed invention (through the polypeptides they encode). It is well-known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small. Brenner et al., Proceedings of the National Academy of Sciences USA, 1998, 95:6073-6078. Given homology in excess of 40% over more than 70 amino acid residues, the probability that the polypeptide coded for by the claimed polynucleotides is related to the CC chemokines hJE-2/MCP-2 and MCP-3 is, accordingly, very high. Moreover, MCPP has the conserved and defining cysteine residues of the CC chemokines at residues Cys19, Cys44, Cys45, Cys69, and Cys85 (e.g., at page 5, lines 31-33; and Figure 2). In combination, these facts provide more than enough evidence to demonstrate a reasonable probability that the utility of the CC chemokine proteins can be imputed to the polynucleotides of the claimed invention (through the polypeptide they encode).

The Patent Office must accept the Applicants' demonstration that the homology between the polypeptide coded for by the claimed invention and the CC chemokines hJE-2/MCP-2 and MCP-3 demonstrates utility by a reasonable probability unless the Patent Office can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt utility. See *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Patent Office has not provided sufficient evidence or sound scientific reasoning to the contrary.

While the Patent Office has cited literature identifying some of the difficulties that may be involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case. Skolnick et al., Nature Biotechnology, 2000, 18:283-287. Importantly, this article does not contradict Brenner's basic rule that sequence homology in excess of

40% over 70 or more amino acid residues yields a high probability of functional homology as well. Brenner et al., Proceedings of the National Academy of Sciences USA, 1998, 95:6073-6078. More importantly, nor does it contradict the fact that the identification of the polypeptide encoded by the claimed polynucleotides using a combination of independent methods provides compelling scientific evidence that the polypeptide has the biological functions of a CC chemokine protein. At most, this article stands for the proposition that it is difficult to make predictions about function with certainty. The standard applicable in this case is not, however, proof to certainty, but rather proof to reasonable probability.

D. Objective evidence corroborates the utilities of the claimed invention

There is in fact no restriction on the kinds of evidence a Patent Examiner may consider in determining whether a "real-world" utility exists. "Real-world" evidence, such as evidence showing actual use or commercial success of the invention, can demonstrate conclusive proof of utility. *Raytheon v. Roper*, 220 USPQ2d 592 (Fed. Cir. 1983); *Nestle v. Eugene*, 55 F.2d 854, 856, 12 USPQ 335 (6th Cir. 1932). Indeed, proof that the invention is made, used or sold by any person or entity other than the patentee is conclusive proof of utility. *United States Steel Corp.* v. *Phillips Petroleum Co.*, 865 F.2d 1247, 1252, 9 USPQ2d 1461 (Fed. Cir. 1989).

Over the past several years, a vibrant market has developed for databases containing all expressed genes (along with the polypeptide translations of those genes), in particular genes having medical and pharmaceutical significance such as the instant sequence. (Note that the value in these databases is enhanced by their completeness, but each sequence in them is independently valuable.) The databases sold by Applicants' assignee, Incyte, include exactly the kinds of information made possible by the claimed invention, such as tissue and disease associations. Incyte sells its database containing the claimed sequences and millions of other sequences, throughout the scientific community, including to pharmaceutical companies who use the information to develop new pharmaceuticals.

Both Incyte's customers and the scientific community have acknowledged that Incyte's databases have proven to be valuable in, for example, the identification and development of drug candidates. As Incyte adds information to its databases, including the information that can be generated

only as a result of Incyte's invention of the claimed polynucleotides, the databases become even more powerful tools. Thus the claimed invention adds more than incremental benefit to the drug discovery and development process.

Customers can, moreover, purchase the claimed SEQ ID NO:2 polynucleotide directly from Incyte, saving the customer the time and expense of isolating and purifying or cloning the polynucleotide for research uses such as those described *supra*.

III. The Office Action's Rejections Are Without Merit

Rather than responding to the evidence demonstrating utility, the Office Action attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotides are not "specific and substantial asserted" utilities (Office Action, March 21, 2003; page 5). The Office Action is incorrect both as a matter of law and as a matter of fact.

A. The precise biological role or function of an expressed polynucleotide is not required to demonstrate utility

The Office Action's primary rejection of the claimed invention is based on the ground that, without information as to the precise "biological role" of the claimed invention, the claimed invention's utility is not sufficiently specific. According to the Office Action, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. The Office Action would require, in addition, that the Applicants provide a specific and substantial interpretation of the results generated in any given expression analysis.

It may be that specific and substantial interpretations and detailed information on biological function are necessary to satisfy the requirements for publication in some technical journals, but they are not necessary to satisfy the requirements for obtaining a United States patent. The relevant question is not, as the Office Action would have it, whether it is known how or why the invention works, *In re Cortwright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999), but rather whether the invention provides an "identifiable benefit" in presently available form. *Juicy Whip Inc.* v. *Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999). If the benefit exists, and there is a substantial likelihood the invention

provides the benefit, it is useful. There can be no doubt, particularly in view of the Bedilion Declaration (at, *e.g.*, ¶¶ 10 and 15), that the present invention meets this test.

The threshold for determining whether an invention produces an identifiable benefit is low. *Juicy Whip*, 185 F.3d at 1366. Only those utilities that are so nebulous that a person of ordinary skill in the art would not know how to achieve an identifiable benefit and, at least according to the PTO guidelines, so-called "throwaway" utilities that are not directed to a person of ordinary skill in the art at all, do not meet the statutory requirement of utility. Utility Examination Guidelines, 66 Fed. Reg. 1092 (Jan. 5, 2001).

Knowledge of the biological function or role of a biological molecule has never been required to show real-world benefit. In its most recent explanation of its own utility guidelines, the PTO acknowledged so much (66 F.R. at 1095):

> [T]he utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have specific and substantial utility because, *e.g.*, it hybridizes near a disease-associated gene or it has gene-regulating activity.

By implicitly requiring knowledge of biological function for any claimed nucleic acid, the Office Action has, contrary to law, elevated what is at most an evidentiary factor into an absolute requirement of utility. Rather than looking to the biological role or function of the claimed invention, the Office should have looked first to the benefits it is alleged to provide.

B. Membership in a class of useful products can be proof of utility

Despite the uncontradicted evidence that the claimed polynucleotides encode a polypeptide in the CC chemokine protein family, the Office Action refused to impute the utility of the members of the CC chemokine protein family to MCPP. The Office Action of March 21, 2003 takes the position that, unless Applicants can identify which particular biological function within the class of CC chemokine proteins is possessed by MCPP, utility cannot be imputed. To demonstrate utility by membership in the class of CC chemokine proteins, the Office would require that all CC chemokine proteins possess a "common" utility.

There is no such requirement in the law. In order to demonstrate utility by membership in a class, the law requires only that the class not contain a substantial number of useless members. So long as the class does not contain a substantial number of useless members, there is sufficient likelihood that the claimed invention will have utility, and a rejection under 35 U.S.C. § 101 is improper. That is true regardless of how the claimed invention ultimately is used and whether or not the members of the class possess one utility or many. *See Brenner* v. *Manson*, 383 U.S. 519, 532 (1966); *Application of Kirk*, 376 F.2d 936, 943 (CCPA 1967).

Membership in a "general" class is insufficient to demonstrate utility only if the class contains a sufficient number of useless members such that a person of ordinary skill in the art could not impute utility by a substantial likelihood. There would be, in that case, a substantial likelihood that the claimed invention is one of the useless members of the class. In the few cases in which class membership did not prove utility by substantial likelihood, the classes did in fact include predominately useless members. *E.g.*, *Brenner* (man-made steroids); *Kirk* (same); *Natta* (man-made polyethylene polymers).

The Office Action addresses MCPP as if the general class in which it is included is not the CC chemokine protein family, but rather all polynucleotides or all polypeptides, including the vast majority of useless theoretical molecules not occurring in nature, and thus not pre-selected by nature to be useful. While these "general classes" may contain a substantial number of useless members, the CC chemokine protein family does not. The CC chemokine protein family is sufficiently specific to rule out any reasonable possibility that MCPP would not also be useful like the other members of the family.

Because the Office Action has not presented any evidence that the class of CC chemokine proteins has any, let alone a substantial number, of useless members, the Office Action must conclude that there is a "substantial likelihood" that the MCPP encoded by the claimed polynucleotides is useful. It follows that the SEQ ID NO:2 polynucleotide also is useful.

Even if the Office Action's "common utility" criterion were correct – and it is not – the CC chemokine protein family would meet it. It is undisputed that known members of the CC chemokine protein family are proteins involved in generating gradients of chemoattractant factors which activate, and may cause the proliferation of, specific cell types such as monocytes, macrophages, basophils, eosinophils, T lymphocytes, and fibroblasts. A person of ordinary skill in the art need not know any

more about how the claimed invention participates in the generation of gradients of chemoattractant factors to use it, and the Office Action presents no evidence to the contrary. Instead, the Office Action makes the conclusory observation that a person of ordinary skill in the art would need to know whether, for example, any given CC chemokine protein generates a gradient of chemoattractant factors which activates any particular cell type. The Office Action then goes on to assume that the only use for MCPP absent knowledge as to how the CC chemokine protein actually works is further study of MCPP itself.

Not so. As demonstrated by Applicants, knowledge that MCPP is a CC chemokine protein is more than sufficient to make it useful for the diagnosis and treatment of cancer and inflammatory disorders. Indeed, MCPP has been shown to be expressed in breast, lung, lymphocyte, macrophage, bladder tumor, NIDDM pancreas, and rheumatoid synovium tissues of humans. The Patent Office must accept these facts to be true unless the Office can provide evidence or sound scientific reasoning to the contrary. But the Patent Office has not done so.

C. The uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself

The Office Action's rejection of the claims at issue is tantamount to a rejection on the ground that the use of an invention as a tool for research is not a "substantial" use. Because the Office Action's rejection assumes a substantial overstatement of the law, and is incorrect in fact, it must be withdrawn.

There is no authority for the proposition that use as a tool for research is not a substantial utility. Indeed, the Patent Office itself has recognized that just because an invention is used in a research setting does not mean that it lacks utility (M.P.E.P. § 2107.01):

> Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the specific invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm.

The Patent Office's actual practice has been, at least until the present, consistent with that approach. It has routinely issued patents for inventions whose only use is to facilitate research, such as DNA ligases. These are acknowledged by the Patent Office's Training Materials to be useful, as are polynucleotide sequences used, for example, as markers.

The subset of research uses that are not "substantial" utilities is limited. It consists only of those uses in which the claimed invention is to be an **object** of further study, thus merely inviting further research on the invention itself. This follows from *Brenner*, in which the U.S. Supreme Court held that a process for making a compound does not confer a substantial benefit where the only known use of the compound was to be the object of further research to determine its use. *Id.* at 535. Similarly, in *Kirk*, the Court held that a compound would not confer substantial benefit on the public merely because it might be used to synthesize some other, unknown compound that would confer substantial benefit. *Kirk*, 376 F.2d at 940, 945. ("What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.") Nowhere do those cases state or imply, however, that a material cannot be patentable if it has some other, additional beneficial use in research.

As used in toxicology testing, drug discovery, and disease diagnosis, the claimed invention has a beneficial use in research other than studying the claimed invention or its protein products. It is a tool, rather than an object, of research. The data generated in gene expression monitoring using the claimed invention as a tool is **not** used merely to study the claimed polynucleotide itself, but rather to study properties of tissues, cells, and potential drug candidates and toxins. Without the claimed invention, the information regarding the properties of tissues, cells, drug candidates and toxins is less complete (Bedilion Declaration at ¶ 15).

The use of the claimed invention as a research tool in toxicology testing is specific and substantial. While it is true that all polynucleotides expressed in humans have utility in toxicology testing based on the property of being expressed at some time in development or in the cell life cycle, this basis for utility does not preclude that utility from being specific and substantial. A toxicology test using any particular expressed polynucleotide is dependent on the **identity** of that polynucleotide, not on its biological function or its disease association. The results obtained from using any particular human-

expressed polynucleotide in toxicology testing is specific to both the compound being tested and the polynucleotide used in the test. **No two human-expressed polynucleotides are interchangeable for toxicology testing** because the effects on the expression of any two such polynucleotides will differ depending on the identity of the compound tested and the **identities** of the two polynucleotides. It is not necessary to know the biological functions and disease associations of the polynucleotides in order to carry out such toxicology tests. Therefore, at the very least, the claimed polynucleotides are specific controls for toxicology tests in developing drugs targeted to other polynucleotides, and are clearly useful as such.

As an example, any histone gene expressed in humans can be used in a specific and substantial toxicology test in drug development. A histone gene may not be suitable as a target for drug development because disruption of such a gene may kill a patient. However, a human-expressed histone gene is surely an excellent subject for toxicology studies when developing drugs **targeted to other genes**. A drug candidate which alters expression of a histone gene is toxic because disruption of such a pervasively-expressed gene would have undesirable side effects in a patient. Therefore, when testing the toxicology of a drug candidate targeted to another gene, measuring the expression of a histone gene is a good measure of the toxicity of that candidate, particularly in *in vitro* cellular assays at an early stage of drug development. The utility of any particular human-expressed histone gene in toxicology testing is specific and substantial because a toxicology test using that histone gene cannot be replaced by a toxicology test using a different gene, including any other histone gene. This specific and substantial utility requires no knowledge of the biological function or disease association of the histone gene.

The claimed invention has numerous additional uses as a research tool, each of which alone is a "substantial utility." These include diagnostic assays (Specification, e.g., at pages 22-23), chromosomal mapping (e.g., at pages 26-27), etc.

D. The Office Action failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility of the claimed invention

Based principally on citations to scientific literature identifying some of the difficulties involved in predicting protein function, the Office Action rejected the pending claims on the ground that the

Applicants cannot impute utility to the claimed invention based on the homology between the encoded polypeptide, MCPP, and another polypeptide undisputed by the Office Action to be useful. The Office Action's rejection is both incorrect as a matter of fact and as a matter of procedural law.

As demonstrated in § II.C, *supra*, the literature cited by the Office Action is not inconsistent with the Applicants' proof of homology by a reasonable probability. It may show that Applicants cannot prove function by homology with **certainty**, but Applicants need not meet such a rigorous standard of proof. Under the applicable law, once the Applicants demonstrate a *prima facie* case of homology, the Patent Office must accept the assertion of utility to be true unless the Patent Office comes forward with evidence showing a person of ordinary skill would doubt the asserted utility could be achieved by a reasonable probability. See *In re Brana*, 51 F.3d at 1566; *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974). The Patent Office has not made such a showing and, as such, the Patent Office's rejection should be withdrawn.

In the present case, the Office Action contends that the degree of amino acid identity among MCPP and other CC chemokine proteins is insufficient to establish that MCPP is a member of the CC chemokine protein family and thus shares the same utilities. The Office Action attempted to support this assertion with the teachings of Skolnick et al. (Nat. Biotechnol., 2000, 18:283-287), of record and addressed below. However, this reference fails to support the outstanding rejections.

In support of Applicants' use of amino acid sequence homology to reasonably predict the utility of the polypeptide encoded by the claimed polynucleotides, Applicants provide the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078). Through exhaustive analysis of a dataset of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 40% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 70 residues, and that 30% identity is a reliable threshold between two sequences aligned over at least 150 residues (Brenner et al., page 6076). Therefore, the 63% sequence identity between SEQ ID NO:1 and hJE-2/MCP-2, and the 62% sequence identity between SEQ ID NO:1 and MCP-3, over 109 amino acid residues, exceeds the threshold proposed by Brenner et al., and SEQ ID NO:1 is a true CC chemokine protein

by these criteria. Since these criteria are based on a dataset of homologous proteins with shared structural and functional features, one of ordinary skill in the art would likewise expect SEQ ID NO:1 to possess the evolutionarily conserved structural and functional characteristics of the hJE-2/MCP-2 and MCP-3 proteins. Hence the "reasonable correlation" standard as set by case law has been met.

The use of such sequence comparisons to predict protein function is supported by Bork (Genome Res., 2000, 10:398-400). The Bork reference discloses a 70% accuracy rate in bioinformatics-based predictions (e.g., in Table 1 on page 399). This more than meets the legal standard of utility, which requires only that one of skill in the art would **more likely than not** believe the utility of the claimed invention. For predicting functional features by homology, Table 1 of Bork discloses a 90% accuracy rate, even greater than the 70% rate for all bioinformatics predictions.

The Examiner cites the Skolnick reference as evidence that "[t]he state of the art is such that functional information can be automatically derived from structural information only to a limited extent . . . Skolnick et al also state that knowledge of the overall structure of domain family is still not enough to confidently assign function to a protein" (Office Action, March 21, 2003; page 7). However, the Office Action misinterprets the findings of Skolnick et al. The Skolnick reference is directed toward the use of "structural" genomics in gene function analysis, wherein the term "structural" refers to three-dimensional atomic structures of proteins. Skolnick et al. make a distinction between the use of structural analysis and the use of sequence analysis in functional annotation. For example, Skolnick et al. state that "structural information can aid in the detection of errors, can in some cases provide general functional information, and can augment **any functional information provided by sequence analysis**" (Skolnick et al., page 286, 1st column, 3rd paragraph; emphasis added). The Office Action's use of the Skolnick reference is inapt because the biological functions of the MCPP polypeptide have been assigned based on the analysis of sequences, not structures.

Furthermore, the Patent Office's assertions that structural analysis is "not enough to confidently assign function" to polypeptides, and that functional information can be derived "only to a limited extent" ignore the general findings of the Skolnick reference. In this regard, Skolnick et al. state that "recent studies have shown that assignment of a protein's biochemical function can also be achieved by scanning its structure for a match to the geometry and chemical identity of a known active site.

Importantly, this approach can use low-resolution structures provided by contemporary structure prediction methods. When applied to genomes, structural information (either experimental or predicted) is likely to play an important role in high-throughput function assignment" (Skolnick et al., page 283, in the Abstract). Therefore, Skolnick et al. are advocating the use of structural analysis to assign protein function, despite limitations such as those that the Patent Office has focused on. Because Skolnick et al. teach that, in general, structural analysis is a good way of assigning protein function, one of skill in the art would understand that a biological function assigned in such a way would **more likely than not** be correct. Therefore, such an assignment of biological function would be one way in which to satisfy the utility requirement of 35 U.S.C. § 101.

The reference cited in the Office Action shows that there may be difficulties and errors involved in predicting protein function by homology. However, this reference does not contradict the fact that such methods are accurate more often than not. As such, one of skill in the art would **more likely than not** believe that MCPP had the utilities of the family of CC chemokine proteins.

There is, in addition, further evidence that the polypeptide encoded by the claimed polynucleotides has the biological functions of the CC chemokine protein family. For example, the specification discloses that MCPP has the conserved and defining cysteine residues of the CC chemokines at residues Cys19, Cys44, Cys45, Cys69, and Cys85 (e.g., at page 5, lines 31-33; and Figure 2). The conservation of cysteine residues which are a characteristic of the CC chemokine family provides independent confirmation of the results of the sequence comparison between MCPP and hJE-2/MCP-2 and MCP-3. These features of MCPP have not been adequately considered by the Patent Office. The disclosure of the instant application shows that a relationship between MCPP and CC chemokine proteins is justified, and that one of skill in the art would reasonably conclude that MCPP has the biological functions of CC chemokine proteins based on objective criteria. Therefore, the subject application has adequately disclosed at least one utility of the claimed invention based on the biological function of MCPP as a CC chemokine protein. These utilities are in addition to the well established utilities of MCPP in toxicology testing and drug discovery, which are not dependent on the specific biological function of MCPP.

As the cited evidence is completely insufficient to support the rejections of the claims, the outstanding rejections must be withdrawn for this reason alone. The only relevant evidence of record shows that a person of ordinary skill in the art would not doubt that the polypeptide encoded by the claimed polynucleotides is in fact a member of the family of CC chemokine proteins, which are known to have specific utility.

IV. By Requiring the Patent Applicant to Assert a Particular or Unique Utility, the Patent Examination Utility Guidelines and Training Materials Applied by the Patent Office Misstate the Law

There is an additional, independent reason to withdraw the rejections: to the extent the rejections are based on Revised Interim Utility Examination Guidelines (64 FR 71427, December 21, 1999), the final Utility Examination Guidelines (66 FR 1092, January 5, 2001) and/or the Revised Interim Utility Guidelines Training Materials (USPTO Website www.uspto.gov, March 1, 2000), the Guidelines and Training Materials are themselves inconsistent with the law.

The Training Materials, which direct the Examiners regarding how to apply the Utility Guidelines, address the issue of specificity with reference to two kinds of asserted utilities: "specific" utilities, which meet the statutory requirements, and "general" utilities, which do not. The Training Materials define a "specific utility" as follows:

> A [specific utility] is *specific* to the subject matter claimed. This contrasts to *general* utility that would be applicable to the broad class of invention. For example, a claim to a polynucleotide whose use is disclosed simply as "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

The Training Materials distinguish between "specific" and "general" utilities by assessing whether the asserted utility is sufficiently "particular," *i.e.*, unique (Training Materials at page 52) as compared to the "broad class of invention." (In this regard, the Training Materials appear to parallel the view set forth in Stephen G. Kunin, Written Description Guidelines and Utility Guidelines, 82

J.P.T.O.S. 77, 97 (Feb. 2000) ("With regard to the issue of specific utility the question to ask is whether or not a utility set forth in the specification is *particular* to the claimed invention.").)

Such "unique" or "particular" utilities never have been required by the law. To meet the utility requirement, the invention need only be "practically useful," *Natta*, 480 F.2d 1 at 1397, and confer a "specific benefit" on the public. *Brenner*, 383 U.S. at 534. Thus incredible "throwaway" utilities, such as trying to "patent a transgenic mouse by saying it makes great snake food," do not meet this standard. Karen Hall, Genomic Warfare, The American Lawyer 68 (June 2000) (quoting John Doll, Chief of the Biotech Section of USPTO).

This does not preclude, however, a general utility, contrary to the statement in the Training Materials where "specific utility" is defined (page 5). Practical real-world uses are not limited to uses that are unique to an invention. The law requires that the practical utility be "definite," not particular. *Montedison,* 664 F.2d at 375. Applicants are not aware of any court that has rejected an assertion of utility on the grounds that it is not "particular" or "unique" to the specific invention. Where courts have found utility to be too "general," it has been in those cases in which the asserted utility in the patent disclosure was not a practical use that conferred a specific benefit. That is, a person of ordinary skill in the art would have been left to guess as to how to benefit at all from the invention. In *Kirk*, for example, the CCPA held the assertion that a man-made steroid had "useful biological activity" was insufficient where there was no information in the specification as to how that biological activity could be practically used. *Kirk*, 376 F.2d at 941.

The fact that an invention can have a particular use does not provide a basis for requiring a particular use. See *Brana*, *supra* (disclosure describing a claimed antitumor compound as being homologous to an antitumor compound having activity against a "particular" type of cancer was determined to satisfy the specificity requirement). "Particularity" is not and never has been the *sine qua non* of utility; it is, at most, one of many factors to be considered.

As described *supra*, broad classes of inventions can satisfy the utility requirement so long as a person of ordinary skill in the art would understand how to achieve a practical benefit from knowledge of the class. Only classes that encompass a significant portion of nonuseful members would fail to meet the utility requirement. *Supra* § III.B (*Montedison,* 664 F.2d at 374-375).

The Training Materials fail to distinguish between broad classes that convey information of practical utility and those that do not, lumping all of them into the latter, unpatentable category of "general" utilities. As a result, the Training Materials paint with too broad a brush. Rigorously applied, they would render unpatentable whole categories of inventions heretofore considered to be patentable, and that have indisputably benefitted the public, including the claimed invention. See *supra* § III.B. Thus the Training Materials cannot be applied consistently with the law.

III. Utility/enablement rejection under 35 U.S.C. § 112, first paragraph

Claims 3-7, 9, 10, 12, 13, 46, and 57 were rejected under 35 U.S.C. § 112, first paragraph, based on the alleged lack of utility under 35 U.S.C. § 101.

The rejection set forth in the Office Action is based on the assertions discussed above, i.e., that the claimed invention lacks patentable utility. To the extent that the rejection under 35 U.S.C. § 112, first paragraph, is based on the improper allegation of lack of patentable utility under 35 U.S.C. § 101, it fails for the same reasons.

IV. Enablement rejection of "variants" under 35 U.S.C. § 112, first paragraph

Claims 3-7, 9, 10, 12, 13, 46, and 57 were rejected under 35 U.S.C. § 112, first paragraph, based on the allegation that the specification does not describe the subject matter of the invention in such a way as to enable one of skill in the art to make and/or use the claimed variants and fragments (Office Action, March 21, 2003; page 8). In particular, the Office Action asserts that the practice of the claimed invention would require "a substantial inventive contribution on the part of the practitioner which would involve the determination of those nucleotide sequences of the disclosed naturally-occurring nucleic acid encoding the MCPP polypeptide, which are required for functional and structural integrity of the MCPP polypeptide" (Office Action, March 21, 2003; page 9). Such, however, is not the case.

With respect to this rejection, claims 4, 5, 10, and 57 are directed to inventions defined by SEQ ID NO:1 and/or SEQ ID NO:2. Claim 4 is drawn to polynucleotides encoding polypeptides comprising SEQ ID NO:1, claims 5 and 57 are drawn to polynucleotides comprising SEQ ID NO:2,

and claim 10 is drawn to methods of making polypeptides comprising SEQ ID NO:1. The Office Action's rejection is based on the alleged lack of enablement of polynucleotide and polypeptide **variants**, and thus should not apply to claims 4, 5, 10, and 57. For at least this reason, this rejection of claims 4, 5, 10, and 57 should be withdrawn.

With respect to the claimed variants, the Office Action asserts that "the instant specification would still fail to adequately describe and enable an isolated polynucleotide encoding a protein that is at least 90% identical to the polypeptide of SEQ ID NO:1" (Office Action, March 21, 2003; page 9). Note that claim 3, for example, recites not only that the polynucleotides encode polypeptides which are at least 90% identical to SEQ ID NO:1, but also that they have "**a naturally occurring amino acid sequence**." Through the process of natural selection, nature will have determined the appropriate amino acid sequences. Given the information provided by SEQ ID NO:1 (the amino acid sequence of MCPP) and SEQ ID NO:2 (the polynucleotide sequence encoding MCPP), one of skill in the art would be able to routinely obtain "a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1." For example, the identification of relevant polynucleotides could be performed by hybridization and/or PCR techniques that were well-known to those skilled in the art at the time the subject application was filed and/or described throughout the specification of the instant application. See, e.g., page 21, line 36 to page 22, line 14; and Example VI at page 36. Thus, one skilled in the art need not make and test vast numbers of polynucleotides that encode polypeptides based on the amino acid sequence of SEQ ID NO:1, or vast numbers of polynucleotides based on the polynucleotide sequence of SEQ ID NO:2. Instead, one skilled in the art need only screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature. By adjusting the nature of the probes or nucleic acids (i.e., non-conserved, conserved, or highly conserved) and the conditions of hybridization (maximum, high, intermediate, or low stringency), one can obtain variant polynucleotides of SEQ ID NO:2 which, in turn, will allow one to make the variant polypeptides of SEQ ID NO:1 recited by the present claims using conventional techniques of recombinant protein production.

Furthermore, it is not necessary to determine "those nucleotide sequences of the disclosed naturally-occurring nucleic acid encoding the MCPP polypeptide, which are required for functional and structural integrity of the MCPP polypeptide" in order to make and/or use the recited polynucleotides encoding polypeptide variants of SEQ ID NO:1. The identity of particular nucleotide sequences which contribute to the functional and structural integrity of MCPP has no bearing on the ability of a skilled artisan to screen a cDNA library or use appropriate PCR conditions to identify relevant polynucleotides, and their encoded polypeptides, that already exist in nature, without undue experimentation. Moreover, it is irrelevant whether any of the claimed polynucleotides encode polypeptide variants which have any biological functions at all. One of skill in the art would still know how to make and use such polynucleotides, without undue experimentation. For example, polynucleotides which encode nonfunctional polypeptide variants of SEQ ID NO:1 could be used to detect polynucleotides which encode the polypeptide of SEQ ID NO:1 by, for example, hybridization and/or PCR techniques. It is not necessary for a polynucleotide to encode a functional polypeptide for one of skill in the art to be able to use that polynucleotide without undue experimentation.

In addition, the Office Action has ignored the fact that the recited polynucleotide variants have specific, substantial, and credible utilities in, for example, toxicology testing in drug discovery (discussed in § II, above). One of skill in the art would know that, as a part of such toxicology testing, the recited polynucleotide variants could be used to detect toxic side effects of drug candidates targeted to other polynucleotides. Therefore, the claimed polynucleotides meet the enablement requirement of 35 U.S.C. § 112, first paragraph, based at least on the well-known, specific, and substantial utilities of expressed, naturally occurring, polynucleotides in toxicology testing.

As set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971):

> The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought

> to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Contrary to the standard set forth in *Marzocchi*, the Office Action has failed to provide any **reasons** why one would doubt that the guidance provided by the present Specification would enable one to make and use the recited polynucleotides encoding polypeptide variants of SEQ ID NO:1 or the recited polynucleotide variants of SEQ ID NO:2. Hence, a *prima facie* case for non-enablement has not been established with respect to the recited variants of SEQ ID NO:1 and SEQ ID NO:2.

For at least the above reasons, withdrawal of this rejection is requested.

V. Written description rejections under 35 U.S.C. § 112, first paragraph

Claims 3-7, 9, 10, 12, 13, 46, and 57 were rejected under 35 U.S.C. § 112, first paragraph, as being based on a specification which allegedly fails to reasonably convey to one of skill in the art that the Applicants had possession of the claimed invention at the time the application was filed. The Office Action asserts that "[t]he specification and claims do not indicate what distinguishing attributes shared by the members of the genus" (Office Action, March 21, 2003; page 10). This rejection is traversed.

With respect to this rejection, claims 4, 5, 10, and 57 are directed to inventions defined by SEQ ID NO:1 and/or SEQ ID NO:2. Claim 4 is drawn to polynucleotides encoding polypeptides comprising SEQ ID NO:1, claims 5 and 57 are drawn to polynucleotides comprising SEQ ID NO:2, and claim 10 is drawn to methods of making polypeptides comprising SEQ ID NO:1. The Office Action's rejection is based on the alleged lack of written description of polynucleotide and polypeptide **variants** and **fragments**, and thus should not apply to claims 4, 5, 10, and 57. For at least this reason, this rejection of claims 4, 5, 10, and 57 should be withdrawn.

The requirements necessary to fulfill the written description requirement of 35 U.S.C. § 112, first paragraph, are well established by case law.

> . . . the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention

> is, for purposes of the "written description" inquiry, *whatever is now claimed.* *Vas-Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)

Attention is also drawn to the Patent and Trademark Office's own "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, which provide that:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics. What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail. If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met. [footnotes omitted]

Thus, the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one skilled in the art.

A. The specification provides an adequate written description of the claimed "variants" and "immunogenic fragments" of SEQ ID NO:1 and SEQ ID NO:2.

The subject matter encompassed by claims 3-7, 9, 10, 12, 13, 46, and 57 is either disclosed by the specification or is conventional or well known to one skilled in the art.

First note that the "variant" language of independent claim 3 recites a polynucleotide encoding "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" and the "variant" language of independent claim 12 recites "a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2." Furthermore, the "immunogenic fragment" language of independent claim 3 recites a polynucleotide encoding "an immunogenic fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the immunogenic fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1."

The amino acid sequence of SEQ ID NO:1 and the polynucleotide sequence of SEQ ID NO:2 are explicitly disclosed in the specification. See, for example, the Sequence Listing and Figures 1A, 1B, and 2. Variants of SEQ ID NO:1 and SEQ ID NO:2 are described in the Specification at, for example, page 4, lines 17-32; page 5, line 39 to page 6, line 2; page 6, lines 5-27; page 7, line 28 to page 8, line 13; page 10, lines 8-26; and page 22, lines 6-11. Fragments of SEQ ID NO:1 and SEQ ID NO:2 are described in the Specification at, for example, page 2, lines 31-34; page 4, lines 2-5 and lines 35-38; page 6, lines 28-34; page 10, lines 5-8; page 15, lines 34 to page 16, line 1; page 17, lines 23-32; page 18, lines 16-25; page 20, lines 33-37; page 21, lines 19-20; page 36, lines 2-9 and lines 27-37; and page 37, line 35 to page 38, line 9. Furthermore, methods to determine the immunogenicity of polypeptide fragments by measuring the specific binding of antibodies are disclosed in the Specification at, for example, page 19, lines 31-39; and page 38, lines 10-13.

One of ordinary skill in the art would recognize polynucleotide sequences which are variants having a polynucleotide sequence at least 90% identical to SEQ ID NO:2, or which encode polypeptide variants having an amino acid sequence at least 90% identical to SEQ ID NO:1. Given any naturally occurring polynucleotide sequence, it would be routine for one of skill in the art to recognize whether it was a variant of SEQ ID NO:2, or whether it encoded a variant of SEQ ID NO:1. Accordingly, the specification provides an adequate written description of the recited polynucleotide variants of SEQ ID NO:2 and polynucleotides encoding polypeptide variants of SEQ ID NO:1.

One of ordinary skill in the art would recognize polynucleotide sequences which are fragments of SEQ ID NO:2, which encode polypeptide sequences which are fragments of SEQ ID NO:1, or which encode polypeptide sequences which are fragments comprising at least 15 contiguous amino acid residues of SEQ ID NO:1. The information provided by SEQ ID NO:1 and SEQ ID NO:2 provides the necessary framework for the recited fragments -- to recite every possible fragment would needlessly clutter the application. Furthermore, it would be routine for one of skill in the art to determine whether any particular fragment of SEQ ID NO:1 had immunogenic activity, using methods disclosed in the specification and/or known in the art. Accordingly, the specification provides an adequate written description of polynucleotides encoding the recited immunogenic fragments of SEQ ID NO:1.

1. The present claims specifically define the claimed genus through the recitation of chemical structure

Court cases in which "DNA claims" have been at issue (which are hence relevant to claims to proteins encoded by the DNA) commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. For example, in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993), the court stated that:

> If a conception of a DNA requires a precise definition, such as by structure, formula, chemical name or physical properties, as we have held, then a description also requires that degree of specificity.

In a number of instances in which claims to DNA have been found invalid, the courts have noted that the claims attempted to define the claimed DNA in terms of functional characteristics without any reference to structural features. As set forth by the court in *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997):

> In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function.

Thus, the mere recitation of functional characteristics of a DNA, without the definition of structural features, has been a common basis by which courts have found invalid claims to DNA. For example, in *Lilly*, 43 USPQ2d at 1407, the court found invalid for violation of the written description requirement the following claim of U.S. Patent No. 4,652,525:

> 1. A recombinant plasmid replicable in procaryotic host containing within its nucleotide sequence a subsequence having the structure of the reverse transcript of an mRNA of a vertebrate, which mRNA encodes insulin.

In *Fiers*, 25 USPQ2d at 1603, the parties were in an interference involving the following count:

> A DNA which consists essentially of a DNA which codes for a human fibroblast interferon-beta polypeptide.

Party Revel in the *Fiers* case argued that its foreign priority application contained an adequate written description of the DNA of the count because that application mentioned a potential method for

isolating the DNA. The Revel priority application, however, did not have a description of any particular DNA structure corresponding to the DNA of the count. The court therefore found that the Revel priority application lacked an adequate written description of the subject matter of the count.

Thus, in *Lilly* and *Fiers*, nucleic acids were defined on the basis of functional characteristics and were found not to comply with the written description requirement of 35 U.S.C. § 112; *i.e.*, "an mRNA of a vertebrate, which mRNA encodes insulin" in *Lilly*, and "DNA which codes for a human fibroblast interferon-beta polypeptide" in *Fiers*. In contrast to the situation in *Lilly* and *Fiers*, the claims at issue in the present application define polynucleotides and polypeptides in terms of chemical structure, rather than functional characteristics. For example, the language of independent claims 3 and 12 recites chemical structure to define the claimed genus:

> 3. An isolated polynucleotide encoding a polypeptide selected from the group consisting of:
> a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,
> b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1,
> c) a fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has chemotactic activity, and
> d) an immunogenic fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the immunogenic fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1.
>
> 12. An isolated polynucleotide selected from the group consisting of:
> a) a polynucleotide comprising the polynucleotide sequence of SEQ ID NO:2,
> b) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 90% identical to the polynucleotide sequence of SEQ ID NO:2,
> c) a polynucleotide complementary to a polynucleotide of a),
> d) a polynucleotide complementary to a polynucleotide of b), and
> e) an RNA equivalent of a)-d).

From the above it should be apparent that the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. In the present case, there is no reliance merely on a description of functional characteristics of the polynucleotides and polypeptides. The polynucleotides defined by the claims of the present application recite structural

features, and cases such as *Lilly* and *Fiers* stress that the recitation of structure is an important factor to consider in a written description analysis of claims of this type. By failing to base the written description inquiry "on whatever is now claimed," the Patent Office failed to provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in *Lilly* and *Fiers*.

The Patent Office Guidelines indicate that evidence that Applicants were in possession of the claimed invention can include "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, **or** some combination of such characteristics" (P.T.O. Guidelines, *supra*; emphasis added). The claimed polynucleotides have been described by chemical structure (e.g., relation of the recited polynucleotides to SEQ ID NO:2, relation of the recited polypeptides to SEQ ID NO:1), physical properties (e.g., occurrence in nature of the recited variant sequences), and chemical properties (e.g., immunogenic activity of the recited fragments). Therefore, the written description requirement has been met.

2. The present claims do not define a genus which is "highly variant"

Furthermore, the claims at issue do not describe a genus which could be characterized as "highly variant." Available evidence illustrates that, rather than being a large variable genus, the claimed genus is of narrow scope.

In support of this assertion, the Examiner's attention is directed to the enclosed reference by Brenner et al. ("Assessing sequence comparison methods with reliable structurally identified distant evolutionary relationships," Proc. Natl. Acad. Sci. USA, 1998, 95:6073-6078). Through exhaustive analysis of a data set of proteins with known structural and functional relationships and with <90% overall sequence identity, Brenner et al. have determined that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues (Brenner et al., pages 6073 and 6076). Furthermore, local identity is particularly important in this case for assessing the significance of the alignments, as Brenner et al. further report that ≥40% identity over at least 70 residues is reliable in signifying homology between proteins (Brenner et al., page 6076).

The present application is directed, *inter alia*, to polynucleotides encoding CC chemokine proteins, including polynucleotides encoding CC chemokine proteins related to the amino acid sequence of SEQ ID NO:1. In accordance with Brenner et al., naturally occurring molecules may exist which could be characterized as CC chemokine proteins and which have as little as 40% identity over at least 70 residues to SEQ ID NO:1. The "variant language" of the present claims recites a polynucleotide encoding "a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1" (note that SEQ ID NO:1 has 109 amino acid residues). This variation is far less than that of polynucleotides encoding all potential CC chemokine proteins related to SEQ ID NO:1, i.e., those CC chemokine proteins having as little as 40% identity over at least 70 residues to SEQ ID NO:1.

3. The state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications

In the *Lilly* case, claims of U.S. Patent No. 4,652,525 were found invalid for failing to comply with the written description requirement of 35 U.S.C. § 112. The '525 patent claimed the benefit of priority of two applications, Application Serial No. 801,343 filed May 27, 1977, and Application Serial No. 805,023 filed June 9, 1977. In the *Fiers* case, party Revel claimed the benefit of priority of an Israeli application filed on November 21, 1979. Thus, the written description inquiry in those cases was based on the state of the art at essentially the "dark ages" of recombinant DNA technology.

The present application has a priority date of July 15, 1996. Much has happened in the development of recombinant DNA technology in the 18 or so years from the time of filing of the applications involved in *Lilly* and *Fiers* and the present application. For example, the technique of polymerase chain reaction (PCR) was invented. Highly efficient cloning and DNA sequencing technology has been developed. Large databases of protein and nucleotide sequences have been compiled. Much of the raw material of the human and other genomes has been sequenced. With these remarkable advances, one of skill in the art would recognize that, given the sequence information of SEQ ID NO:1 and SEQ ID NO:2, and the additional extensive detail provided by the subject application, the present inventors were in possession of the claimed polynucleotide variants, and polynucleotides encoding the recited immunogenic fragments, at the time of filing of this application.

4. Summary

The Office Action failed to base the written description inquiry "on whatever is now claimed." Consequently, the Office Action did not provide an appropriate analysis of the present claims and how they differ from those found not to satisfy the written description requirement in cases such as *Lilly* and *Fiers*. In particular, the claims of the subject application are fundamentally different from those found invalid in *Lilly* and *Fiers*. The subject matter of the present claims is defined in terms of the chemical structure of SEQ ID NO:1 and SEQ ID NO:2. The courts have stressed that structural features are important factors to consider in a written description analysis of claims to nucleic acids and proteins. In addition, the genus of polynucleotides defined by the present claims is adequately described, as evidenced by Brenner et al. Furthermore, there have been remarkable advances in the state of the art since the *Lilly* and *Fiers* cases, and these advances were given no consideration whatsoever in the position set forth by the Office Action.

For at least the reasons set forth above, the specification provides an adequate written description of the claimed subject matter, and this rejection should be withdrawn.

VI. Rejection of "chemotactic activity" under 35 U.S.C. § 112, second paragraph

Claims 3-7, 9, 10, 46, and 57 were rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the recitation of the phrase "has chemotactic activity" is indefinite. The Office Action asserts that "it is unclear as to which type of cells the protein is chemotactic" (Office Action, March 21, 2003; page 12). This rejection is traversed.

With respect to this rejection, claims 4, 5, 10, 46, and 57 are directed to inventions defined by SEQ ID NO:1 and/or SEQ ID NO:2. Claim 4 is drawn to polynucleotides encoding polypeptides comprising SEQ ID NO:1, claims 5 and 57 are drawn to polynucleotides comprising SEQ ID NO:2, claim 10 is drawn to methods of making polypeptides comprising SEQ ID NO:1, and claim 46 is drawn to microarrays comprising polynucleotides based on SEQ ID NO:2. The Office Action's rejection is based on the alleged indefiniteness of polynucleotides encoding **fragments having**

chemotactic activity, and thus should not apply to claims 4, 5, 10, 46, and 57. For at least this reason, this rejection of claims 4, 5, 10, 46, and 57 should be withdrawn.

Under the second paragraph of 35 U.S.C. § 112, the standard for "definiteness" is that the claims define patentable subject matter with a **reasonable** degree of precision and particularity. See *In re Miller*, 169 USPQ 597, 599 (CCPA 1971); *In re Moore*, 169 USPQ 236, 238 (CCPA 1971). See also M.P.E.P. § 706.03(d). In this regard, the Supreme Court has indicated that the primary purpose of claim language is to give "fair" notice of what would constitute the infringement of a claim. See *United Carbon Co. v. Binny & Smith Co.*, 317 U.S. 228, 55 USPQ 381 (1942). In other words, the basic purpose of 35 U.S.C. § 112, second paragraph is to require a claim to reasonably apprise those skilled in the art of the scope of the invention defined by that claim and give fair notice of what constitutes infringement of the claim. See *Antonius v. Pro Group Inc.*, 217 USPQ 875, 877 (6th Cir.1983). The present claims meet the legal standards required by 35 U.S.C. § 112, second paragraph.

Claim 3 recites polynucleotides which encode polypeptide fragments which have chemotactic activity. The specification provides methods to measure chemotactic activity at, for example, page 37, lines 17-33. The specification also provides examples of cell types which can be assayed using the disclosed method:

> Specificity of the chemoattraction is determined by performing the assay on fractionated populations of cells such as enriched populations of **neutrophils, mononuclear cells, monocytes or lymphocytes** obtained by density gradient centrifugation. Specific **T cell** populations can be purified using CD8+ and CD4+ specific antibodies for negative selection. (Specification, page 37, lines 29-33; emphasis added)

Furthermore, the specification states that CC chemokines can have chemotactic activity for "specific cell types such as monocytes, macrophages, basophils, eosinophils, T lymphocyte, and fibroblasts" (e.g., at page 1, lines 28-31). Thus, a skilled artisan would reasonably understand that the recited polypeptide fragments have chemotactic activity for one or more specific cell types, and would also know what types of cells the recited fragments could have chemotactic activity for.

For at least the above reasons, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

VII. Rejection of "immunogenic fragment" under 35 U.S.C. § 112, second paragraph

Claims 3-7, 9, 10, 46, and 57 were rejected under 35 U.S.C. § 112, second paragraph, based on the allegation that the recitation of the phrase "immunogenic fragment" is indefinite. The Office Action asserts that the recited immunogenic fragments "can encompass any six amino acids or the entire protein" (Office Action, March 21, 2003; page 12). This rejection is traversed.

With respect to this rejection, claims 4, 5, 10, 46, and 57 are directed to inventions defined by SEQ ID NO:1 and/or SEQ ID NO:2. Claim 4 is drawn to polynucleotides encoding polypeptides comprising SEQ ID NO:1, claims 5 and 57 are drawn to polynucleotides comprising SEQ ID NO:2, claim 10 is drawn to methods of making polypeptides comprising SEQ ID NO:1, and claim 46 is drawn to microarrays comprising polynucleotides based on SEQ ID NO:2. The Office Action's rejection is based on the alleged indefiniteness of polynucleotides encoding **immunogenic fragments**, and thus should not apply to claims 4, 5, 10, 46, and 57. For at least this reason, this rejection of claims 4, 5, 10, 46, and 57 should be withdrawn.

To expedite prosecution, claim 3 has been amended such that the recited immunogenic fragments encoded by the claimed polynucleotides comprise "at least 15 contiguous amino acid residues of SEQ ID NO:1." Support for this amendment can be found in the specification at, for example, page 35, lines 1-5. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides encoding immunogenic fragments comprising fewer than 15 contiguous amino acid residues of SEQ ID NO:1. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that claim 3, as amended, and dependent claims 4-7, 9, and 10, recite patentable subject matter.

For at least the above reasons, withdrawal of this rejection under 35 U.S.C. § 112, second paragraph, is requested.

VIII. Rejections under 35 U.S.C. § 102(b)

Claims 3 and 6-9 were rejected under 35 U.S.C. § 102(b) because the recited polynucleotides encoding a polypeptide comprising an immunogenic fragment of SEQ ID NO:1 are allegedly anticipated by U.S. Patent No. 5,278,287 (Rollins et al., January 11, 1994). The Office Action asserts that U.S. Patent No. 5,278,287 discloses a polynucleotide which "meets the limitations of a polynucleotide of instant claims 3, 6-9 of the instant invention" (Office Action, March 21, 2003; page 13). This rejection is traversed.

Applicants respectfully point out that claim 8 was canceled in the Response to Restriction Requirement mailed on January 14, 2003 (see, e.g., page 1 of the Response). The cancellation of claim 8 is acknowledged on page 2 of the instant Office Action at § 1. Since claim 8 has been canceled, the instant rejection applies to claims 3, 6-7, and 9.

To expedite prosecution, claim 3 has been amended such that the recited immunogenic fragments encoded by the claimed polynucleotides comprise "at least 15 contiguous amino acid residues of SEQ ID NO:1." Support for this amendment can be found in the specification at, for example, page 35, lines 1-5. By this amendment, Applicants expressly do not disclaim equivalents of the invention which could include polynucleotides encoding immunogenic fragments comprising fewer than 15 contiguous amino acid residues of SEQ ID NO:1. Applicants do not concede to the Patent Office position; Applicants are amending the claims solely to obtain expeditious allowance of the instant application. While not conceding to the Patent Office position, it is believed that claim 3, as amended, and dependent claims 6-7 and 9, recite patentable subject matter. Therefore, withdrawal of this rejection is requested.

CONCLUSION

In light of the above amendments and remarks, Applicants submit that the present application is fully in condition for allowance, and request that the Examiner withdraw the outstanding rejections. Early notice to that effect is earnestly solicited.

If the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, Applicants invite the Examiner to contact the undersigned at (650) 621-8581.

Applicants believe that no fee is due with this communication. However, if the USPTO determines that a fee is due, the Commissioner is hereby authorized to charge Deposit Account No. **09-0108.**

Respectfully submitted,

INCYTE CORPORATION

Date: June 18, 2003.

Terence P. Lo, Ph.D.
Limited Recognition (37 C.F.R. § 10.9(b)) attached
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 3 has been amended as follows:

3. (Twice Amended) An isolated polynucleotide encoding a polypeptide selected from the group consisting of:

a) a polypeptide comprising the amino acid sequence of SEQ ID NO:1,

b) a polypeptide comprising a naturally occurring amino acid sequence at least 90% identical to the amino acid sequence of SEQ ID NO:1,

c) a fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the fragment has chemotactic activity, and

d) an immunogenic fragment of the polypeptide having the amino acid sequence of SEQ ID NO:1, wherein the immunogenic fragment comprises at least 15 contiguous amino acid residues of SEQ ID NO:1.